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Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

January 25, 2008

Dear Administrator:

On behalf of the Flavor and Fragrance High Production Volume Consortia, I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on "Alicyclic Aldehydes-HMPCC". HMPCC is an acronym for 3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (lyral), CAS No. 31906-04-4.

The Alicyclic Aldehyde Consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for chemical substances under the Chemical Right-to-Know Program. Since 1999, the companies that are current members of the Consortium have supported the collection and review of available test data, development of test plans and robust summaries, and conducted additional testing for HMPCC.

Based on our initial recommendations for testing and the peer-reviewed comments of the EPA, the Alicyclic Aldehyde Consortium of the Flavor and Fragrance High Production Volume Consortia (FFHPVC) is pleased to submit the following revised test plan and robust summaries for HMPCC. The revised test plan and robust summaries contain additional data on existing studies and the results of additional studies on ecotoxicity, toxicity, physiochemical properties and environmental fate that are related to the questions and comments made by the EPA in its letter dated 7/1/2003. This letter contains responses to the specific comments made by the EPA. These responses taken together with the inclusion of new study data and other information constitute the key changes to the original test plan and robust summaries.

Based on these additional data, the Alicyclic Aldehyde Consortium concludes that the current test plan and robust summaries for this category is now complete. The experimental and model data for

physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent and provide a comprehensive basis upon which to evaluate the hazard potential of 3- and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde. A summary of the key hazard data for HMPCC has been included in this letter (see Table 1).

We consider that the test plan and robust summaries for this category are final and have no plans to provide additional data. The EPA comprehensive comments provided the necessary guidance to complete the test plan for this category. The collaboration between the Alicyclic Aldehyde Consortium and the Environmental Protection Agency in the Chemical "Right to Know" Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.

Technical Contact Person for FFHPVC

Summary of Key Hazard Data for Alkyl-substituted Cyclohexyl Derivatives

Endpoint	Substance/Surrogate[1]	Value/Range[2]	Reference
Physical Properties			
Vapor Pressure	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	<0.001 kPa (25 °C)	FMA, 1996
Partition Coefficient	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	2.1 (OECD 117)	Givaudan-Roure,1996
Water Solubility	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	<186 mg/l at 20 °C	WSKOW (2000)
Environmental Fate			
Biodegradation	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	41.2 % (28 days)-not biodegradable. (OECD 301B) 62 % (28 days)-not readily biodegradable (OECD 301F)	Quest, 1996 Givaudan, 1995
Ecotoxicity			
Fish	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	LC50=11.8 mg/L	Ward, 2003
Aquatic Invertebrates	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	48-hr LC50 = 76mg/L	Waggy, 1986
Aquatic Plants	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	72 hr EC50=25.4 mg/L (av specifc growth rate); 72-hr EC50=13.7mg/L (number of cells/mL); 72-hr EC50=13.8 mg/L (AUC). The 72-hr NOEC=5.95 mg/L	Boeri, 2003
Human Health			
Repeat Dose (route)	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	28-d LOAEL: 1000 mg/kg bw/d and NOAEL=150mg/kg bw/d (OECD No. 407 Guideline Study)	Dunster et al., 2006
Reproductive/Developme	3- and 4-(4-hydroxy-4-	Offspring NOAEL=25 mg/kg	Hoberman, 2006

[1] Surrogate is a structurally related substance include a metabolic product or precursor of the named substance

[2] Experimental value or values for a substance or group of substances in the chemical category

ntal	methyl pentyl)-3-cyclohexene-1-carboxaldehyde	bw/d Maternal NOAEL=100 mg/kg bw/d (OECD 415)	
Developmental(route)	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	At 500 mg/kg bw dosing: through gestation- no dermal effects through lactation-skin sloughing	Lewis, 2007
in vitro Genotoxicity[3]	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	-(AMS) -(AMS) -(AMS) - (ABS)	Cocchiara, 2001 Wagner and Klug, 1999 Takasago, 1999 Gudi R. and Schadly, E.H., 2000
in vivo Genotoxicity[4]	3- and 4-(4-hydroxy-4-methyl pentyl)-3-cyclohexene-1-carboxaldehyde	-(MN	Cocchiara, 2001 Gudi R., 2000

[3] (-), no significant evidence; (+/-), equivocal evidence; (+), positive evidence of genotoxicity
[4] (-), no significant evidence; (+/-), equivocal evidence; (+), positive evidence of genotoxicity

EPA Comments on Chemical RTK HPV Challenge Submission:
3- and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC)

SUMMARY OF EPA COMMENTS

The sponsor, the Alicyclic Aldehyde Consortium of the Flavor and Fragrance High Production Volume Consortia, submitted a test plan and robust summaries to EPA for HMPCC (CAS No. 31906-04-4) in December 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 25, 2003. The submission also contained robust summaries for related chemicals: 7-hydroxycitronellal, 4-isopropenyl-1-cyclohexene-1-carboxaldehyde, 2,4-dimethyl-3-cyclohexenecarboxaldehyde, 4-isopropenyl-1-cyclohexenecarbinol (perillyl alcohol) and 7-hydroxycitronellol.

EPA has reviewed this submission and has reached the following conclusions:

1.Physicochemical Properties. EPA agrees with the submitter's proposed testing for vapor pressure, octanol/water partition coefficient, and water solubility. The submitter needs to provide measured melting point data for HMPCC.

Response: Experimental data on Kow, vapor pressure, and solubility have been included in the robust summaries and test plan. Based on the repeated efforts of the manufacturer to obtain a reliable melting point and inability to obtain a solid sample, calculated melting point will be used. We emphasize that a melting point for this mixture is at this time is unnecessary to the overall hazard evaluation of the substance.

2. Environmental Fate. The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. Even though this chemical lacks hydroxyzable groups, the submitter needs to indicate this fact in robust summary format. EPA agrees with the submitter's proposed testing plan for biodegradation.

Response: Biodegradation data for HMPCC are available from two studies.

3. Health Effects. Adequate data are available for the acute, repeated-dose, and genetic toxicity endpoints for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposal to conduct testing for reproductive and developmental toxicity. The submitter needs to address deficiencies in the robust summaries.

Response: The sponsors have supported the performance of a 28-day oral gavage study (OECD 407), a one-generation reproduction study (OECD 415), and special developmental study to evaluation the adverse dermal effects observed at the two highest dose levels in the OECD 415 study.

4. Ecological Effects. The aquatic invertebrate toxicity data are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's plan to conduct acute toxicity tests on fish and algae.

Response: Fish and algal studies have been performed using HMPCC in OECD Guideline 203 and 201 studies.

EPA COMMENTS ON THE HMPCC CHALLENGE SUBMISSION

General

The submission consists of data for a mixture of 3-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (30%) and 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (70%). The data for structurally similar chemicals have been included to support the available information on this substance. The submission did not include CAS numbers for analogs.

Based on the additional data for HMPCC, data on the analogs is provides additional but not key category information.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

EPA agrees with the submitter's proposed testing for vapor pressure, octanol/water partition coefficient, and water solubility. The boiling point data are adequate for the purposes of the HPV Challenge Program.

Melting point. EPA agrees that because HMPCC is a mixture, the determination of a melting point for either the 3- or the 4-isomer is not relevant (and estimated melting points such as that provided in the test plan are generally unreliable). The submitter needs to provide measured melting point data on the commercial mixture, following OECD TG 102 (as the commercial product is described as a viscous liquid at ambient temperature, the cited freezing point method may be appropriate).

Response: The manufacturers were unable to obtain a sample appropriate to perform a melting point. Since HMPCC is manufacturer and used as a mixture, melting point information is not key to the hazard evaluation of this substance.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposed testing plan for biodegradation. When testing for biodegradation, EPA strongly recommends that the submitter follow OECD TG 301.

Response: The sponsors have performed OECD 301B and OECD 301F biodegradation studies. These data are consistent.

Stability in water. Although this chemical lacks hydroxyzable groups, the submitter needs to indicate this fact in robust summary format.

Response: A robust summary on stability in water has been included in the robust summaries.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproduction/developmental toxicity).

Adequate data are available for the acute, repeated-dose, and genetic toxicity endpoints for the purposes of the HPV Challenge Program. EPA agrees with the submitter's proposal to conduct testing for reproductive and developmental toxicity. The submitter needs to address deficiencies in the robust summaries.

Response: Additional in vitro and in vivo genotoxicity data and a repeat dose dose on HMPCC have been performed by the sponsor. These have been included in the revised test plan and robust summaries.

Repeated-Dose Toxicity. No data were submitted for HMPCC, but the reliance on analogs is justified by the metabolism data provided in section 2.5 of the test plan showing relatively rapid absorption of related substances and rapid excretion of metabolites. Of the studies submitted, NCI's 4-isopropenyl-1-cyclohexenecarbinol (perillyl alcohol) 90-day gavage study addresses this endpoint.

Response: Data has now been provided for HMPCC.

Reproductive/Developmental Toxicity. No data were submitted. EPA agrees with the submitter's plan for testing of HMPCC in a combined screening test for reproduction/developmental toxicity according to OECD TG 421. Although not provided by the submitter, published 14- or 28-day studies of perillyl alcohol showed testicular epithelial degeneration and irreversible testicular atrophy at 900 and 1000 mg/kg/day, respectively. These effects were not seen in the 90-day study in which the highest dose tested was 400 mg/kg/day. EPA suggests consideration of these data when setting up dose levels for the proposed reproduction/developmental toxicity study.

Response: A One generation reproduction study (OECD 415) and an additional developmental study have been performed to evaluation high dose dermal effects (see test plan and robust summaries).

Ecological Effects (fish, invertebrates, and algae).

The submitted acute toxicity data for acute invertebrates are adequate for the purposes of the HPV Challenge program. EPA agrees with the submitter's plan to conduct OECD-compliant acute toxicity tests on fish and algae.

Specific Comments on the Robust Summaries

General comment

Throughout the robust summaries the title substance is HMPCC but often this is not the substance tested. To avoid confusion it is preferable to title each summary with the name of the substance tested and then to identify it as an analog of HMPCC. The summaries should also include CAS numbers for analogs.

Health Effects

Acute Toxicity. The following information is missing from the key study robust summary (Mallory, et al. 1982, Reliability Code 1): test substance purity, time of deaths at each dose, whether body weights were measured and any effects observed. There is a typographical error in the LD_{50} value field; the value is reported as "greater than 5,000 ml/kg bw" and the test was performed up to 6.0 ml/kg bw. The LD_{50} values needs to be reported as mg/kg bw (density of the test material is not provided in the submission).

Response: These data were added if available in the literature.

Repeated-Dose Toxicity. A robust summary for an NCI 90-day gavage study for the analog perillyl alcohol lacks information on test material purity, statistical methods used, and method details such as hematology, clinical chemistry parameters, organ weights and organs evaluated histopathologically. The cited reference for this robust summary is incorrect. Journal of Cellular Biochemistry. 265, 137-148 should be Journal of Cellular Biochemistry. 26 S, 137-148.

Response: The correction has been made.

Genetic Toxicity. The submitter needs to include information on test substance purity.

Response: These data were added if available in the literature.